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## Modulation of P-glycoprotein activity by estramustine is limited by binding to plasma proteins.

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**BACKGROUND.** Estramustine previously has been shown to interact with P-glycoprotein and to restore intracellular accumulation of vinblastine and paclitaxel in cells overexpressing this drug transporter. However, the ability of estramustine to potentiate the cytotoxicities of several drugs was less than that expected. To resolve this apparent discordance, the authors examined the effects of serum on the actions of estramustine. **METHODS.** The cytotoxicities of anticancer drugs with or without estramustine or verapamil toward MCF-7 breast carcinoma cells and a P-glycoprotein-overexpressing subline MCF-7/ADR were determined using the sulforhodamine-binding assay. The extent of intracellular accumulation of [3H]vinblastine and [3H]paclitaxel was determined for each using standard methods, and the binding of radiolabeled drugs to plasma proteins was characterized by equilibrium dialysis. **RESULTS.** Without serum, the sensitivities of MCF-7/ADR cells to several P-glycoprotein-transported drugs were increased by estramustine and verapamil. Conversely, when the cells were treated with a 10% serum, the cytotoxicities of these drugs were increased by verapamil, but not by estramustine. With serum, intracellular accumulation of [3H]vinblastine and [3H]paclitaxel by MCF-7/ADR cells was increased markedly by verapamil and estramustine; however, serum suppressed the effects of estramustine much more strongly than those of verapamil. Equilibrium dialysis experiments demonstrated that [3H]estramustine binds to plasma proteins, predominantly albumin, whereas [3H]paclitaxel binds to albumin and alpha 1-acid-glycoprotein, and [3H]vinblastine binds predominantly to alpha 1-acid-glycoprotein. **CONCLUSION.** Although estramustine can bind to P-glycoprotein, its effectiveness as a reversing agent in vivo likely is limited by binding to plasma proteins.

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